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Short-Limb Dwarfism and Hypertrophic Cardiomyopathy in a Patient With Paternal Isodisomy 14: 45,XY,idic(14)(p11)

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Uniparental disomy (UPD) has been shown to result in specific disorders either due to imprinting and/or homozygosity of mutant alleles. Here we present the findings in a child with paternal UPD14. Ultrasound evaluation was performed at 30 weeks of gestation because of abnormally large uterine size. Pertinent ultrasound findings included polyhydramnios, short limbs, abnormal position of hands, small thorax, and nonvisualization of the fetal stomach. Postnatally the infant was found to have a low birth weight, short birth length, contractures, short limbs, and a small thorax with upslanting ribs. Assisted ventilation and gastrostomy were required. At age 6 months, the infant required hospitalization for hypertrophic cardiomyopathy which responded to Atenolol®. Initial cytogenetic studies demonstrated an apparently balanced de novo Robertsonian translocation involving chromosomes 14 and a karyotype designation of 45,XY,t(14q14q). No indication of mosaicism for trisomy 14 was observed in metaphase spreads prepared from peripheral blood lymphocytes or skin-derived fibroblasts. C-band and fluorescence in situ hybridization results demonstrated that the chromosome was dicentric. DNA analyses showed paternal uniparental isodisomy for chromosome 14. Based on the cytogenetic and DNA results a final karyotype designation of 45,XY,idic(14)(p11) was assigned to this infant with paternal isodisomy of chromosome 14.

KEY WORDS: short-limb dwarfism, uniparental disomy, isochromosome 14

INTRODUCTION

Isochromosomes and balanced Robertsonian translocations associated with uniparental disomy (UPD) have been reported for chromosomes 13 [Slater et al., 1994], 14 [Temple et al., 1991; Wang et al., 1991; Pentao et al., 1992; Antonarakis et al., 1993; Diamond et al., 1993; Healey et al., 1994; Robinson et al., 1994], 15 [Smith and Noel, 1980; Hamabe et al., 1991; Freeman et al., 1992; Smith et al., 1993; Robinson et al., 1994], 21 [Creau-Goldberg et al., 1987; Blouin et al., 1993, 1994; Robinson et al., 1994], and 22 [Robinson et al., 1994; Schinzel et al., 1994]. Two additional cases of presumed UPD22 have been reported [Palmer et al., 1980; Kirkels et al., 1980], based on apparent inheritance of maternal t(22;22); however, genotyping was not performed. Clearly, UPD can cause human disorders. For example, UPD is noted to cause Prader-Willi syndrome due to parental imprinting of genes [Nicholls et al., 1989] and cystic fibrosis due to homozygosity of mutant recessive alleles in the case of isodisomy [Spence et al., 1988]. Only a few cases of UPD14 have been reported and, of these, only two are paternally derived UPD [Wang et al., 1991; Diamond et al., 1993]. Here we describe a third case of paternally derived UPD14 in which all tested polymorphic DNA markers for chromosome 14 were homozygous in the proband.

PATIENT AND METHODS

Clinical Report

The mother of the propositus, a 25-year-old G1 woman with gestational diabetes, was referred for ul-

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trasound evaluation at 30 weeks gestation because her uterine size was abnormally large. There were no prenatal toxic exposures. Polyhydramnios [an amniotic fluid index greater than 24 cm; Carlson et al., 1990] was noted. All limbs were below the 5th centile in length, while the fetal head and abdominal measurements were normal for the gestational age. Additional findings included abnormal position of hands (Fig. 1), a small thorax, and non-visualization of the fetal stomach. Non-visualization of the stomach suggested a swallowing disorder in the fetus as the cause of polyhydramnios.

Two weeks later worsening of polyhydramnios, with a corresponding amniotic fluid index of 56.5 cm, was observed. The stomach was still not seen and the ratio of cardiac to thoracic circumference was 56%, which was suggestive of pulmonary hypoplasia. Labor developed at 34 weeks gestation and proceeded to an uncomplicated vaginal delivery.

Apgar scores were 4 and 5 at 1 and 5 minutes. Vigorous stimulation was required for respiratory effort and the infant was placed on a ventilator. The infant was limp and inactive. The length was 39.5 cm which was below the 3rd centile. The head appeared to be large and there was significant scalp edema. The palpebral fissures were short (5.5 cm; <3rd centile), there were no cataracts, and the fundi were normal. An intact palate was present. The ears were small (2.7 cm; 3rd centile) and mildly dysplastic. The neck was short and broad. The thorax was narrow with a prominent sternum and hypoplastic nipples. Examination of the heart showed a grade II/VI systolic ejection murmur. Pulses were normal. The liver was palpable 3 cm below the right costal margin; there was diastasis recti. The testes were not palpable in the scrotum or inguinal regions; the phallus was normal. The fingers were long (mid-finger 2.7 cm; 97th centile) with mild contractures of the proximal interphalangeal joints (Fig. 2). The thumbs were adducted and the wrists were flexed. The palms were short, with single flexion creases. There were mild contractures of the elbows and knees, and the limbs were short (lower leg 7.5 cm; <3rd centile). Roentgenographs showed a bell-shaped thorax with upslanting ribs (Fig. 3a). The first metacarpals were short. The fibulae were long and the proximal tibial epiphyses were small (Fig. 3b). These physical findings were not suggestive of previously described lethal short-limb dwarfing conditions.

The infant required assisted ventilation for the first 24 hours. Following extubation, the infant had frequent episodes of hypoxia and apnea and was unable to nurse. Abdominal sonography was normal and an upper GI examination documented no obstruction. A gastrostomy tube was placed for feeding and the infant demonstrated good weight gain. Echocardiography showed a small atrial septal defect and a patent ductus arteriosus, which subsequently closed. The aortic valve was asymmetric. Cranial CT and MRI demonstrated prominence of the Sylvian fissure; there were no apparent anomalies of the brain.

At age 4 months, the weight was 3.5 kg (<5th centile), length was 49 cm (<5th centile), and OFC was 36.5 cm (<5th centile). He was alert and active with good color and had brachycephaly, a high-arched palate, small ears, short broad nose, long philtrum, short wide neck, short and narrow thorax and short limbs, with mild contractures at the knees and elbows. The great toes over-rode the second toes. Developmen-

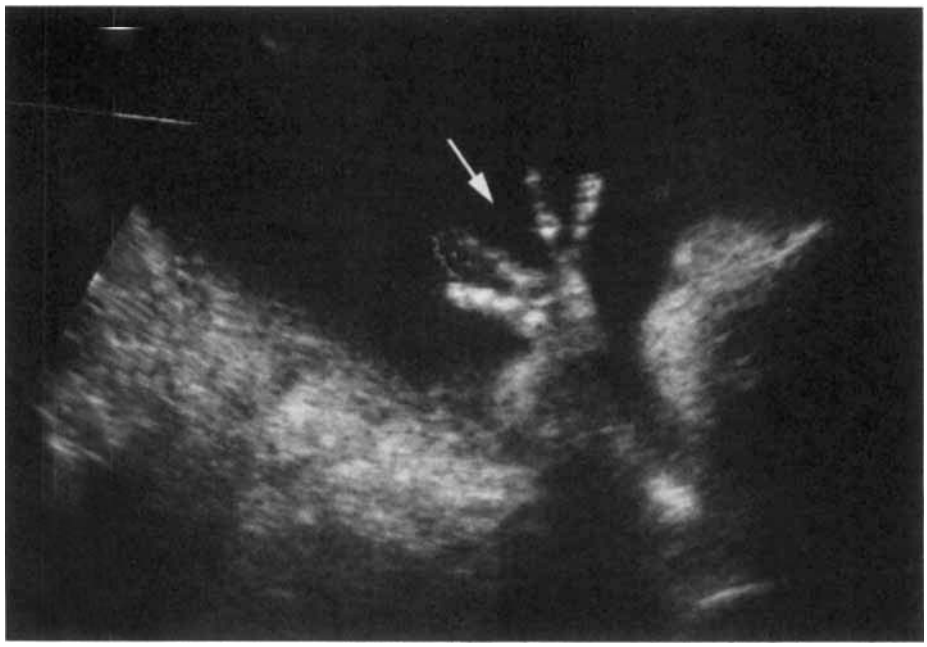

Fig. 1. Ultrasound image obtained at 30 weeks gestational age. Abnormal posture of the fetal hand is apparent (arrow).

Fig. 2. Frontal image of the infant. Long fingers with contractures and unusual facial appearance are evident.

tally, he was responsive, smiled and cooed. He was able to roll from back to side and reached for toys.

At 6 months the infant was hospitalized for congestive heart failure. An endotracheal tube was inserted and the child was placed on a ventilator. An echocardiogram demonstrated obstructive hypertrophic cardiomyopathy. The infant was subsequently treated with Atenolol®. A repeat echocardiogram after 3 days showed improvement with no evidence of obstruction. After 7 days the infant was extubated and subsequently discharged on Atenolol®.

Cytogenetic Studies

Metaphase spreads obtained from peripheral blood lymphocyte cultures of the patient and his parents were G-banded by conventional methods. The patient's lymphocyte metaphase spreads were also C-banded and silver stained by routine procedures. Fibroblasts were grown from a skin biopsy and metaphase spreads prepared for routine G-banding to look for mosaicism. Fluorescence in situ hybridization (FISH) was performed on the patient's lymphocyte-derived metaphase spreads using a commercial (α-satellite probe (D14Z1/D22Z1; Oncor), that hybridizes to chromosomes 14 and 22, according to the manufacturer's recommendations.

DNA Polymorphism Studies

DNA was obtained using standard methods from peripheral blood samples from the patient and each parent. Chromosome 14 polymorphisms were analyzed subsequently to determine the parental origin(s) of the dicentric chromosome 14. Nineteen highly polymorphic dinucleotide repeat polymorphisms spanning chromosome 14 were used. The relative marker locations are shown in Table I as published previously [Shapira et al., 1994]. As a control, two chromosome 20 markers (SRC and D20S117) were used to demonstrate normal biparental inheritance of a non-chromosome 14 marker (data not shown). PCR amplifications were performed using previously published methods [Shaffer et al.,

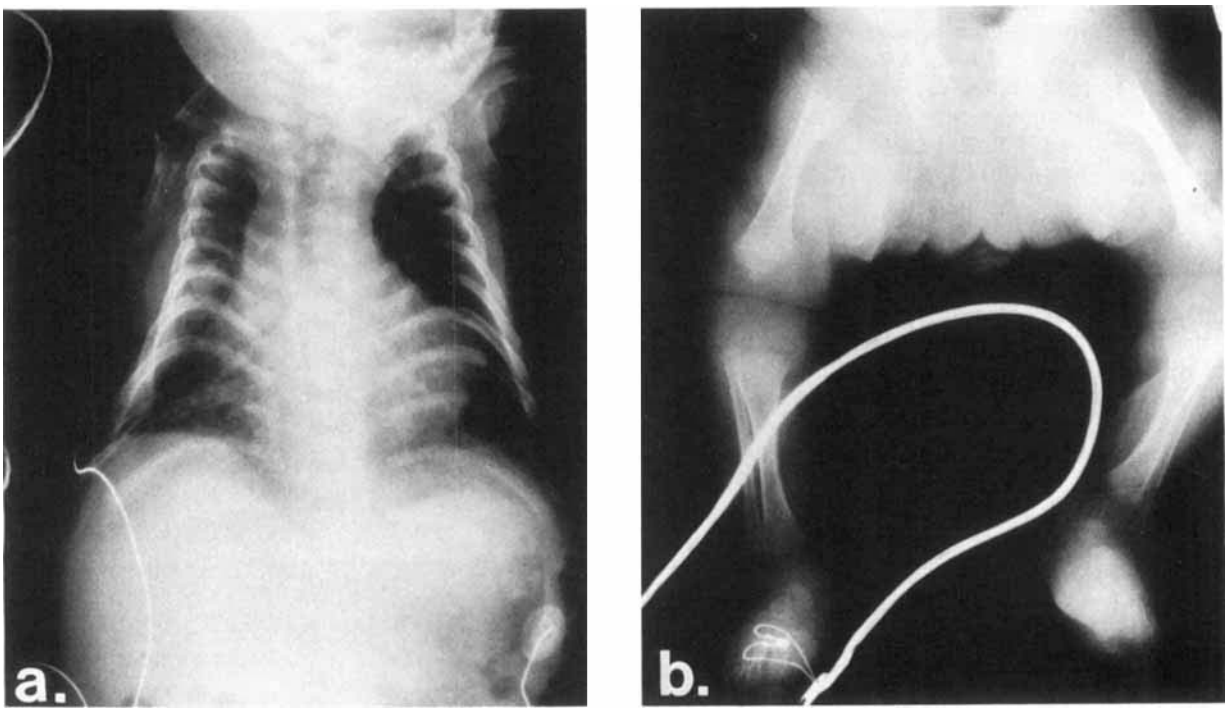

Fig. 3. X-ray images of the propositus. **a:** A small thorax with upslanting ribs was visualized. **b:** Long fibulae and small proximal tibial epiphyses were found in images of the lower extremities.

TABLE I. Results of DNA Analyses for Markers on Chromosome 14*

Locus	Location	Mother	Father	Child	Inheritance
TCRA	14q11.2	11	11	11	Uninformative
TCRD*	14q11.2	11	23	13	Biparental
D14S50	14q11.2	12	12	22	Uninformative
D14S80	14q11.2	12	22	22	Uninformative
D14S54	14q11.2-22	12	22	22	Uninformative
D14S49	14q11.2-22	12	34	44	Paternal
D14S70	14q11.2-22	33	12	22	Paternal
D14S75	14q11.2-22	11	23	22	Paternal
D14S47	14q11.2-22	12	12	11	Uninformative
D14S52	14q21-22	12	12	22	Uninformative
D14S66	14q22-24.3	12	12	11	Uninformative
D14S77	14q22-24.3	34	12	11	Paternal
D14S42	14q24	11	11	11	Uninformative
D14S43	14q24.3	12	11	11	Uninformative
D14S53	14q24.3-32.1	12	12	11	Uninformative
D14S55	14q24.3-32.1	11	12	11	Uninformative
D14S48	14q24.3-32.1	22	12	22	Uninformative
D14S45	14q32.1-32.2	13	12	11	Uninformative
D14S51	14q32.1-32.2	12	23	22	Uninformative

* Results from a monospecific chromosome 14 somatic cell hybrid and extensive EMBL database searches suggest the reported CA repeat is not at the TCRD locus on chromosome 14.

1993b]. Because TCRD was the only chromosome 14 marker that indicated biparental inheritance of chromosome 14, a 14-specific monochromosomal somatic cell hybrid [NA10479; Coreill Cell Repositories; Lugo et al., 1987; Dubois and Naylor, 1993] was used in an attempt to confirm the reported 14q11.2 locus of a CA repeat in the TCRD gene [Jordan et al., 1991].

RESULTS

Initial G-banding studies indicated that the patient had an apparently balanced Robertsonian translocation involving chromosomes 14 (Fig. 4a). Silver staining was negative, while C-banding and FISH (Fig. 4b) indicated a dicentric chromosome. A karyotype designation of 45,XY,dic(14)(p11) was given using this information. The parents had normal chromosomes. No evidence for mosaicism was found in 45 lymphocyte-derived metaphase spreads or 50 fibroblast-derived metaphase spreads.

All polymorphic DNA markers tested except TCRD were homozygous in the propositus. Markers D14S49, D14S70, D14S75, and D14S77 showed inheritance of only paternal alleles (Table I; Fig. 5), consistent with paternal uniparental isodisomy. Exclusive paternal inheritance for distal chromosome 14 could not be confirmed because the seven markers were uninformative. Minimally, the region between D14S49 and D14S77 is paternal in origin and is isodisomic. Thus, a final karyotype designation of 45,XY,idic(14)(p11) was assigned.

A CA repeat in the TCRD gene was the only marker assigned to chromosome 14 [Jordan et al., 1991] demonstrating biparental inheritance. Therefore, DNA prepared from a 14-specific monochromosomal somatic cell hybrid and total human DNA was subjected to PCR amplification with primers specific for the CA repeat reportedly in the TCRD gene. An amplification signal was not detected with DNA prepared from the 14-specific monochromosomal somatic cell hybrid while amplification was detected from total human DNA (data not shown). TCRD has been well characterized with regard to its location at 14q11.2 [Boehm et al., 1988; Isobe et al., 1988; Takihara et al., 1988]; thus it seems unlikely that TCRD itself has been misassigned to chromosome 14. Rather, it seems likely that the CA

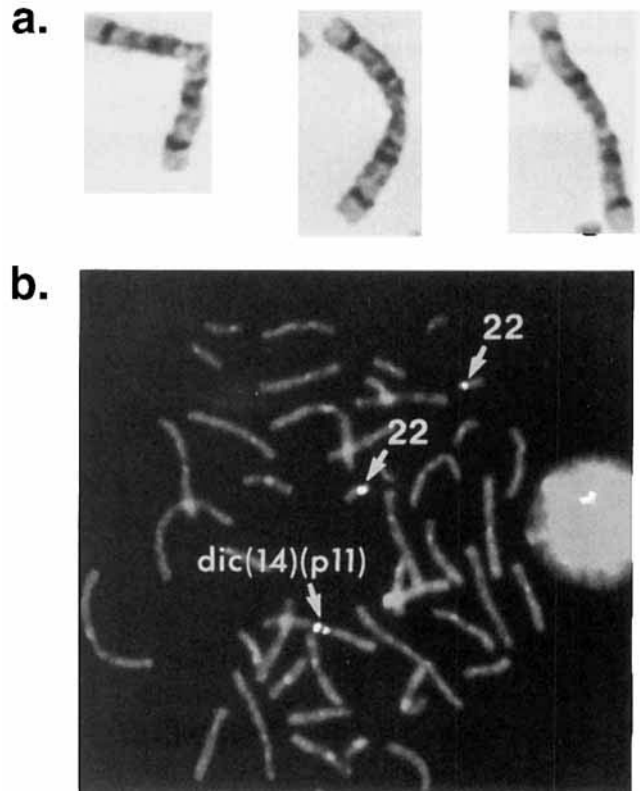

Fig. 4. Cytogenetic analyses. **a:** GTG-banded chromosomes demonstrating an apparently balanced t(14q14q) chromosome. **b:** Hybridization of a metaphase spread with 14/22 α-satellite probe (D14Z1/D22Z1). The translocated chromosome appears dicentric (large arrow).

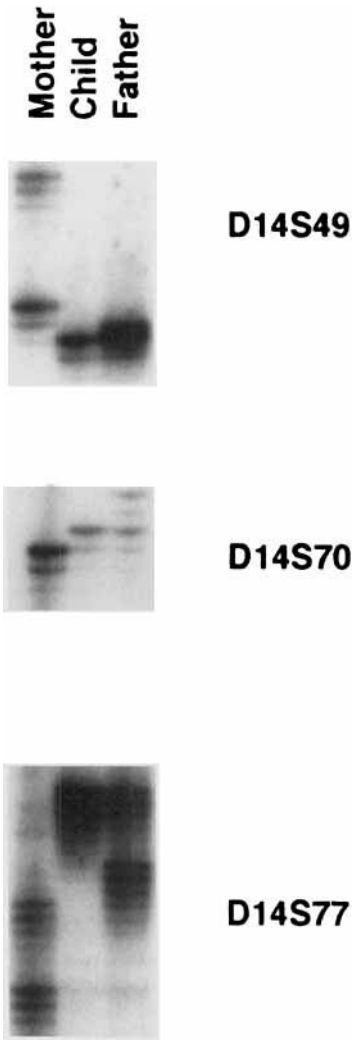

Fig. 5. DNA analyses of chromosome 14 polymorphic markers. Markers D14S49, D14S70, D14S75, and D14S77 showed inheritance of only paternal alleles and no inheritance of maternal alleles which is consistent with paternal disomy.

repeat was misassigned. Furthermore, an extensive search of TCRD genomic sequences in the EMBL database failed to demonstrate the presence of a CA repeat. Because these results suggest the CA repeat is not at the TCRD locus on chromosome 14, these data were not used to determine the parental inheritance of the dic(14)(p11) chromosome.

DISCUSSION

The events that produced this UPD are not known. However, the following possibilities are offered: 1) a monosomic chromosome 14 conceptus formed an isochromosome through duplication, 2) a euploid conceptus duplicated the paternal chromosome 14 as an isochromosome and restored disomy through loss of the maternal chromosome 14, 3) asynapsis and a U-type exchange [de la Chapelle, 1982] produced an isochromosome 14 that resulted in a trisomic conceptus which was rescued by loss of the maternal chromosome 14, and 4) a U-type exchange subsequent to paternal meiotic recombination produced an isochromosome and the resulting trisomic conceptus was rescued by loss of the maternal chromosome 14. All of these scenarios would result in some degree of mosaicism. We did not find any evidence of mocsaicism; therefore, it seems most likely that the first example occurred because monosomic chromosome 14 cells would not survive as long as the trisomic chromosome 14 cells that would be generated in the other three examples. Indeed, Robinson et al. [1994] have suggested that most isochromosomes and Robertsonian translocations are produced postzygotically as somatic events. The chromosome described in this report was dicentric. Both dicentric and monocentric forms of acrocentric-derived isochromosomes have been reported [Shaffer et al., 1991, 1993a, 1994; Slater et al., 1994].

Our patient has several characteristics in common with other paternal UPD14 patients: 1) polyhydramnios, 2) digit contractures, 3) small thorax, 4) abnormal ribs, 5) low birth weight, 6) birth length $\leq$ 10th centile, 7) required gastrostomy, and 8) small ears (Table II). Despite some common findings among paternal UPD14 patients, a clear phenotype for paternal UPD14 is not apparent from these three cases. Although low birth weight and short birth length are observed in maternal and paternal UPD14, there does not appear to be a significant overlap in phenotypes between maternal and paternal UPD14 [Antonarakis et al., 1993; Diamond et al., 1993 Healy et al., 1994; Pentao et al., 1992; Robinson et al., 1994; Sirchia et al., 1994; Wang et al., 1991].

We speculate that the dwarfism described in the current patient may be associated with paternal UPD14. Several growth factor genes and a bone morphogenetic protein have been mapped to chromosome 14. Placental growth factor [Maglione et al., 1991], transforming growth factor β3 [ten Dijke et al., 1988], thyroid stimulating hormone receptor [Gross et al., 1991], and bone morphogenetic protein 4 [Ozkaynak et al., 1990] are potentially interesting with regard to this dwarfing condition because of their physical location on chromosome 14. At this time, it is not possible to determine if the dwarfing is caused by imprinting, homozygosity for a mutant allele, or a mechanism unrelated to UPD14. However, because the other two reported cases of paternal UPD14 did not describe the dwarfing condition seen in our patient, it seems unlikely that imprinting is the mechanism involved.

Our patient developed hypertrophic cardiomyopathy at 6 months. One locus for familial hypertrophic cardiomyopathy has been assigned to chromosome 14 at q11-12 [Jarcho et al., 1989]. Hypertrophic cardiomyopathy is inherited as an autosomal dominant disorder; however, the condition can remain silent until an acute episode causes death of the patient [McKenna and Goodwin, 1981]. A correlation between familial hypertrophic cardiomyopathy and mutations in the β cardiac myosin heavy chain gene has been reported [Geisterfer-Lowrance et al., 1990]. There was no history of cardiomyopathy in the patient's family. It may

TABLE II. Comparison of Findings at Birth Among Three Paternal UPD14 Patients*

Feature	Propositus	Diamond et al. [1993]	Wang et al. [1991]
Polyhydramnios	+	+	NS[a]
Digit contractures	+	+	
Small thorax	+		+
Abnormal ribs	+		+
Low birth weight	+		+
Short birth length	+		+
Required gastrostomy	+	+	
Small ears	+		+
Hygromas			+
Webbed neck			+
Simian creases	+		+
Blepharophimosis/ Short palpebral fissures	+		+
Anteverted nares			+
Protruding philtrum	+		+
Fetal abdominal distention		+	
Puckered lips	+	+	
Hirsute forehead		+	
Retrognathia		+	
Ventral wall hernia		+	
Heart murmur	+		
Undescended testes	+	NA[b]	NA
Short limbs	+		
Required tracheostomy/ endotracheal intubation	+	+	

* +, positive finding.
[a] Prenatal history was not specified.
[b] Not applicable.

only be coincidence that our patient had hypertrophic cardiomyopathy and an abnormality associated with chromosome 14. However, it is also possible that the inherited paternal allele of β cardiac myosin heavy chain was abnormal and is the genetic cause of the cardiomyopathy observed in our patient.

Although undetected mosaicism for trisomy 14 cannot be ruled out, our chromosomal and DNA analyses support the finding of paternal UPD14 as the cause of phenotypic abnormalities in this patient. It appears from this case and others that additional cytogenetic and DNA analysis is warranted in patients with apparently balanced Robertsonian translocations associated with phenotypic abnormalities and no other cause factors can be implicated. Identification of additional cases of paternal UPD14 will facilitate a determination of whether there is a phenotype characteristic of this genetic abnormality.

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NOTE ADDED IN PROOF

Since the submission of this manuscript, a full publication describing the patient by Diamond et al. [1993] has appeared [Papenhausen et al., 1995: Uniparental isodisomy of chromosome 14 in two cases: an abnormal child and a normal adult. Am J Med Genet 59: 271–275].

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